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(56) Documents cited
GBA 2012274
GBA 2011900
GB 1538207
GB 1369249
GB 0775364
Archiv Intern.
Pharmacodynan 145 233-42 (1963)
J. Neurochen 37 837-44 (1981)
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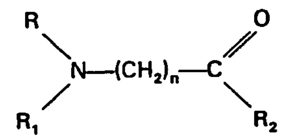
C2C
(71) Applicant
Midit Societe Fiduciaire Enregistree (Liechtenstein),
Vaduz, Liechtenstein
(72) Inventors
Alexis Cordi,
Claude Gillet,
Joseph Roba,
Paul Niebes,
Philippe Janssens de Varebeke,
Georges Lambelin
(74) Agent and/or Address for Service
Boult, Wade & Tennant,
27 Furnival Street,
London EC4A 1PQ

(54) **Derivatives of ω-amino alkanoic acids**

(57) Compounds of the formula I



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for use in treating epilepsy, depression, dyskinesias such as Parkinson's disease, muscular spasms of nervous origin, hypertension, hypotension, sleeping troubles, memory defects, and as anthelminthic and analgesic agents wherein R represents:—

a linear or branched C_2 to C_{12} alkyl radical

a linear or branched C_2 to C_4 alkyl radical substituted by a phenyl or phenoxy nucleus which may be substituted by one or two linear or branched C_1 to C_4 alkyl radicals by one or two linear or branched C_1 to C_4 alkoxy radicals or by one or two halogen atoms

a linear or branched C_2 to C_6 acyl radical substituted by a phenyl nucleus which may be substituted by one or two linear or branched C_1 to C_4 alkyl radicals by one or two linear or branched C_1 to C_4 alkoxy radicals or by one or two halogen atoms.

R_1 represents

hydrogen,

a linear or branched C_2 to C_{11} acyl radical

a linear or branched C_2 to C_6 acyl radical substituted by a phenyl nucleus which may be substituted by one or two linear or branched C_1 to C_4 alkyl radicals by one or two linear or branched C_1 to C_4 alkoxy radicals or by one or two atoms of halogen, such as fluorine, chlorine or bromine,

R_2 represents:—

a hydroxyl group

an alkoxy group R_3O— in which R_3 is a linear or branched C_1 to C_3 alkyl radical;

an amino group; and

n is 3, 4 or 5; or a pharmaceutically or veterinarily acceptable salt thereof.

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Applicants: Mitchell Shirvan et al.
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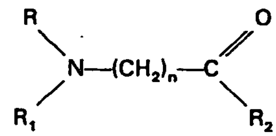
Exhibit 14

SPECIFICATION

Derivatives of ω-amino acids, the preparation and utilisation thereof, and the compositions containing these derivatives

The present invention relates to derivatives of ω-amino acids, the salts of these derivatives, the processes for their preparation and pharmaceutical compositions containing at least one of these derivatives, and the method of their utilisation.

The present invention includes the derivatives of ω-amino acids which respond to the general formula I



I

and the salts of these compounds formed with pharmaceutically utilisable metals, acids or bases.

In the general formula I:—

R represents:—

a linear or branched alkyl radical C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12};

a linear or branched alkyl radical C_2, C_3, C_4, substituted by a phenyl or phenoxy nucleus which may be substituted by one or two linear or branched alkyl radical C_1, C_2, C_3, C_4, by one or two linear or branched alkoxy radicals C_1, C_2, C_3, C_4, or by one or two atoms of halogen such as fluorine, chlorine or bromine;

a linear or branched acyl radical C_2, C_3, C_4, C_5, C_6, substituted by a phenyl nucleus which may be substituted by one or two linear or branched alkyl radicals C_1, C_2, C_3, C_4, by one or two linear or branched alkoxy radicals C_1, C_2, C_3, C_4 or by one or two atoms of halogen such as flourine, chlorine or bromine;

R_1 represents:—

hydrogen;

a linear or branched acyl radical C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11};

a linear or branched acyl radical C_2, C_3, C_4, C_5, C_6 substituted by a phenyl nucleus which may be substituted by one or two linear or branched alkyl radicals C_1, C_2, C_3, C_4 by one or two linear or branched alkoxy radicals C_1, C_2, C_3, C_4 or by one or two atoms of halogen such as fluorine, chlorine or bromine;

R_2 represents:—

a hydroxyl group;

an alkoxy group R_3O—, in which R_3 is a linear or branched alkyl radical C_1, C_2 or C_3;

an amino group (—NH_2);

n possesses the values 3, 4 or 5;

According to a preferred form of the invention the latter has for object compounds of formula I in which:—

R represents:—

a linear or branched alkyl radical C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12};

a linear or branched alkyl radical C_2, C_3, C_4 substituted by a phenyl or phenoxy nucleus which may be substituted by one or two linear or branched alkyl radicals C_1, C_2, C_3, C_4, by one or two linear or branched alkoxy radicals C_1, C_2, C_3, C_4, or by one or two atoms of halogen such as fluorine, chlorine or bromine;

a linear or branched acyl radical C_2, C_3, C_4, C_5, C_6 substituted by a phenyl nucleus which may be substituted by one or two linear or branched alkyl radicals C_1, C_2, C_3, C_4, by one or two linear or branched alkoxy radicals C_1, C_2, C_3, C_4, or by one or two atoms of halogen such as fluorine, chlorine or bromine;

R_1 represents:—

hydrogen;

a linear or branched acyl radical C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11};

a linear or branched acyl radical R_2, C_3, C_4, C_5, C_6 substituted by a phenyl nucleus which may be substituted by one or two linear or branched alkyl radicals C_1, C_2, C_3, C_4, by one or two linear or branched alkoxy radicals C_1, C_2, C_3, C_4 or by one or two atoms of halogen such as fluorine, chlorine or bromine;

R_2 represents:—

a hydroxyl group;

an alkoxy group R_3O— in which R_3 is a linear or branched alkyl radical C_1, C_2 or C_3;

an amino group (—NH_2);

n possesses the values 3, 4 or 5;

when R represents a dodecyl radical and R_1 hydrogen, R_2 does not represent a hydroxyl radical,

when n has the value 4 and when R_2 represents a hydroxyl group and R_1 hydrogen, R does not represent an n-butyl or n-octyl radical,

when n has the value 4 and when R_2 represents an ethoxy group and R_1 hydrogen, R does not represent an ethyl or n-butyl radical,

When R represents an n-butyl radical, R_1 hydrogen and R_2 a methoxy or hydroxyl radical n does not possess the value 3,

when R represents an i-propyl radical, R_1 hydrogen and R_2 a hydroxyl radical, n does not possess the value 5.

According to another preferred form of the invention the latter has for object compounds of formula I in which:—

R represents:

a linear or branched alkyl radical C_2—C_{10};

a linear or branched alkyl radical C_2—C_4 substituted by a phenyl or phenoxy nucleus possibly substituted by a methyl or methoxy radical or by an atom of chlorine;

R_1 represents:—

hydrogen

a linear or branched acyl radical C_2—C_{11};

a linear or branched acyl radical C_2—C_6 substituted by a phenyl nucleus which may be substituted by a methyl or methoxy radical or by an atom of chlorine;

R_2 represents:—

a hydroxyl group;

an alkoxy group R_3O in which R_3 is a linear or branched alkyl radical C_1—C_3;

an amino group;

n possesses the values 3, 4 and 5 —

when n has the value 4 and when R_2 represents a hydroxyl group and R_1 hydrogen, R does not represent an n-butyl or n-octyl radial;

when n has the value 4 and when R_2 represents an ethoxy group and R_1 hydrogen, R does not represent an ethyl or n-butyl radical;

when R represents an n-butyl radical, R_1 hydrogen and R_2 a methoxy or hydroxyl radical, n does not possess the value 3;

when R represents an i-propyl radical, R_1 hydrogen and R_2 a hydroxyl radical, n does not possess the value 5.

According to another preferred form of the invention the latter has for object derivatives of formula I in which:—

R represents:—

a linear or branched acyl radical C_2—C_6 substituted by a phenyl nucleus which may be substituted by a methyl or methoxy radical or an atom of chlorine;

R_1 represents hydrogen;

R_2 represents:—

a hydroxyl group;

an alkoxy group R_3O in which R_3 is a linear or branched alkyl radical C_1—C_3;

an amino group;

n possesses the values 3, 4 and 5.

A preferred class of products of formula I is that in which:

R represents a linear or branched alkyl group C_2—C_{10};

R_1 represents hydrogen;

R_2 represents:—

a hydroxyl group;

an alkoxy group R_3O in which R_3 is a linear or branched alkyl radical C_1—C_3;

an amino group;

n possesses the values 3, 4 and 5;

when n has the value 4 and when R_2 represents a hydroxyl group and R_1 hydrogen, R does not represent an n-butyl or n-octyl radical;

when n has the value 4 and when R_2 represents an ethoxy group and R_1 hydrogen, R does not represent an ethyl or n-butyl radical;

when R represents an n-butyl radical, R_1 hydrogen and R_2 a methoxy or hydroxy radical, n does not possess the value 3;

when R represents an i-propyl radical, R_1 hydrogen and R_2 a hydroxyl radical, n does not possess the value 5.

Another preferred class of products of formula I is that in which:—

R represents:—

a linear or branched alkyl group C_2—C_{10};

a linear or branched acyl group C_2—C_6 substituted by a phenyl nucleus;

R_1 represents hydrogen;

R_2 represents:—

a hydroxyl group;

an alkoxy group R_3O in which R_3 is a linear or branched alkyl radical C_1—C_3;

n possesses the value 3;
when R represents an n-butyl radical, R_2 does not represent a methoxy or hydroxyl radical.

A last preferred class of products of formula I is that in which:—

R represents:—

a linear or branched alkyl radical C_2—C_{10};

a linear or branched acyl radical C_2—C_8 substituted by a phenyl nucleus;

R_1 represents hydrogen;

R_2 represents an amino group (—NH_2);

and n has the value 3.

Examples of compounds according to the invention are:—

4-n-pentylamino butanamide,
5-n-pentylamino pentanamide,
6-n-pentylamino hexanamide,
4-n-pentylamino butanoic acid,
5-(p-tolylacetylamino) pentanamide,
6-n-decylamino hexanamide,
6-[(2-p-chlorophenoxy ethyl) amino] hexanamide,
4-[(N-n-hexyl-N-4-chlorophenylacetyl) amino] butanamide.

If the derivatives of formula I are presented in the form of salts of addition with acids, it is possible to transform them, according to usual processes into free bases or into salts of addition with other acids.

The salts most currently used are salts of addition of non-toxic, pharmaceutically usable acids, formed with appropriate inorganic acids, for example hydrochloric acid, sulphuric acid or phosphoric acid or with appropriate organic acids such as aliphatic, cycloaliphatic, aromatic, araliphatic or heterocyclic carboxylic or sulphonic acids, for example formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, hydrobenzoic, salicylic, phenylacetic, mandelic, embonic, methane-sulphonic, ethane-sulphonic pantothenic, toluene sulphonic, sulphanilic, cyclohexylaminosulphonic, stearic, alginic, β-hydroxy butyric, oxalic, malonic, galactaric, galacturonic acids.

In the case where R_2 represents a hydroxyl group, the derivatives according to the invention can exist in the form either of zwitterion, or of non-toxic and pharmaceutically usable salts or metals or salts of addition with bases.

If the derivatives according to the invention in which R_2 represents a hydroxyl group are obtained in the form of salt, they can be transformed into acid or into other salts according to conventional processes.

These salts can be derived from metals such for example as sodium, potassium, lithium, calcium, magnesium, aluminium, iron, or can be salts of addition with bases such for example as ammonia, or amines such as ethylamine, isopropyl amine, ethanolamine, diethylamine, diethanolamine, triethylamine, or basic amino acids, natural or not, such as lysine, arginine, ornithine.

The compounds of formula I can possess one or more asymmetric carbon atoms and thus are capable of existing in the form of optical or racemic isomers or diasteroisomers; all these forms are part of the present invention.

Thus the derivatives according to the invention can be utilised either in the form of mixtures containing several diasteroisomers, whatever are the relative proportions thereof, or in the form of pairs of enantiomers in equal proportions (racemic mixture) or not, or again in the form of optically pure compounds.

The products according to the invention can be utilised in the treatment of neurological, psychic or cardiovascular troubles such for example as epilepsy, depression, dyskinesias such as Parkinson's disease, muscular spasms of nervous origin, hypertension, hypotension, sleeping troubles, memory defects, and as anthelminthic and analgesic agents.

The invention includes compounds as described when for use in a method of treatment by therapy or surgery practised on the human or animal body.

The invention also includes pharmaceutical or veterinary formulations comprising such a compound formulated for pharmaceutical or veterinary use.

The present invention likewise covers pharmaceutical compositions containing, as active ingredient, at least one compound of the general formula I or a salt, with an additive and/or excipient utilised in Galenical pharmacy.

These compositions are prepared in such manner that they can be administered orally, rectally or parenterally. They can be solids, liquids or gels and can be presented, according to the administration route, in the form of powders, tablets, lozenges, coated tablets, capsules, granules, syrups, suspensions, emulsions, solutions, suppositories or gels. These compositions can likewise include another therapeutic agent having an activity similar to or different from the products of the invention.

In particular, the compounds may be in solution as e.g. sterile water or in an oil such as groundnut oil or ethyl oleate.

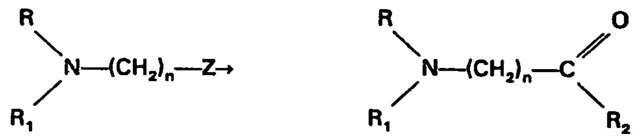
The compounds may be utilised in medical treatment by being administered as dosages of 50 mg to 400 mg by the oral route or 5 mg to 400 mg parenterally and unit dosage formulations may be

provided for this purposes.

The compounds according to the invention are prepared according to processes which form part of the present invention and are defined below. In the cases where the processes give rise to the production of new intermediate compounds, these new compounds, likewise the processes serving for their preparation, also form part of the present invention.

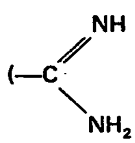
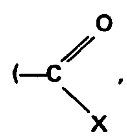
Process A.

According to this manner of procedure, the product II is converted into a derivative of formula I:

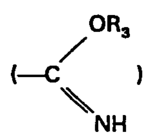


I II

R, R_1, R_2 and n are as defined above and Z represents a group, which, by the action of an appropriate reagent, can be transformed into an amide function, carboxylic acid or ester. Examples of these functions are, among others, the amide function, the carboxylic acid function, the nitrile function, the ester function (—COOR', in which R' represents either R_3, specified above, or an alkyl or phenyl radical substituted in such manner that it activates the ester in relation to the attack of a nucleophile), the amidine function

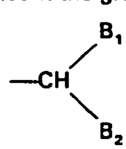
), the acid halide function  ,

where X represents a halogen such as chlorine, bromine or iodine), the anhydride function, the imidate function



or the N-carbonylimidazole group. Z can likewise represent a carboxylic acid precursor group as for example the trihalomethyl grouping (—CX_3, in which X represents an atom of chlorine, bromine or iodine), an oxazoline group, a hydroxymethylene group (—CH_2OH), a formyl group (—CHO) which may or may not be present in a protected form such for example as a dithioacetal, cyclic or not, an α,β-dihydroxyalkyl or alkenyl group (—CHOH—CHOH—R_4 or —CH—CH—R_4 in which R_4 represents a linear alkyl radical C_1—C_{20}), an acetyl group (—CO—CH_3), a 1-hydroxyethyl group (—CHOH—CH_3), a 2-hydroxypropyl-1 group (—CH_2—CHOH—CH_3) or an atom of halogen such as chlorine, bromine or iodine.

The group —CH_2—Z can equally represent the group



in which B_1 and B_2 can be equal or different and represent a function selected from the following series:— nitrile, carboxylic, carbamoyl or alcoxycarbonyl (—$COOR_3$, R_3 having the values given previously).

The passage from the product II to the product I, that is to say the conversion from the group Z or —CH_2—Z into a group (—COR_2), can be realised by conventional reactions very well documented in chemistry, as for example:—

a) conversion of a carboxylic acid into amide.

Several processes permit of effecting this chemical transformation.

For example carboxylic acid can be placed in the presence of ammonia, the pyrolysis of the salt thus formed leads to the amide, likewise the action of a dehydration agent such as P_2O_5.

Another manner of proceedings consists in transforming the carboxylic acid into acid halide then amide by the action of ammonia.

Yet another manner of proceeding consists in placing a carboxylic acid and ammonia into reaction in the presence of a coupling reagent such as is utilised in synthesis of peptides, as for example dicyclohexyl carbodiimide, N-ethyl-N'-3-dimethyl amino propyl carbodiimide, phosphines, phosphites, silicon or titanium tetrachloride.

b) Conversion of a nitrile into amide or acid.

The nitriles can be hydrolysed into amide or acid, either in acid medium or in basic medium. If the hydrolysis is carried out in acid conditions, it is possible to use concentrated sulphuric acid, concentrated aqueous hydrochloric acid, aqueous hydrobromic acid, nitric acid, formic acid in the absence of solvent, acetic acid in the presence of boron trifluoride.

Another manner of converting a nitrile into amide, in acid medium, consists in treating the said nitrile with hydrochloric acid in an alcohol such as ethanol. Thus an intermediate iminoether is formed which is transformed thermally into amide.

If the hydrolysis is effected under basic conditions, one will use for example potassium hydroxide in t-butanol or an aqueous solution of an alkali or earth-alkali metal hydroxide. The presence of oxygenated water facilitates the hydrolysis. The nature of the group formed, an amide or a carboxylic group, depends essentially upon the utilised reaction conditions.

c) Transformation of a nitrile into ester.

This conversion is effected by opposing the nitrile to an alcohol in acid medium. Alcohol or any other inert solvent can be utilised as solvent. Thus an intermediate iminoether is formed which is converted into ester by hydrolysis.

d) Conversion of an ester into amide.

The aminolysis of an ester is is carried out conventionally by opposing ammonia to the ester, either in water or in an inert organic solvent.

e) Conversion of an amidine into amide.

This reaction is carried out principally by acid hydrolysis in aqueous or alcoholic medium. The acid can be inorganic like hydrochloric or sulphuric acid or organic such as acetic acid.

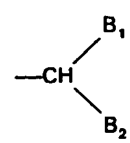
f) Conversion of an acid halide, an anhydride or an N-carbonyl imidazolyl group into a carboxylic acid or alkoxy carbonyl group ($—COOR_3$).

This transformation proceeds easily by opposition of product II to water to form the carboxylic group (hydrolysis reaction) or to an alcohol R_3OH, R_3 being a linear or branched alkyl radical $C_1—C_3$, to form the alkoxycarbonyl groups $—COOR_3$ (alcoholysis reaction).

These reactions take place in the presence of an excess of water or alcohol or with a stoichiometric quantity of these reagents in the presence of an inert solvent. The alcoholysis is advantageously carried out in the presence of a catalyst such as an organic or inorganic acid or base.

g) When the group Z in formula II represents a carboxylic acid precursor such as a trihalomethyl grouping or an oxazoline, the transformation into carboxylic acid is conducted either in water, or in an inert organic solvent in the presence of acid. As acid generally there is used a mineral acid such as the halogenated hydracids, concentrated or dilute sulphuric acid, concentrated or dilute nitric acid, phosphoric acid or an organic acid such as acetic acid.

h) The conversion of the group $—CH_2—Z$, representing the group



in which B_1 and B_2 possess the values given above, into a carboxymethyl group is effected by hydrolysis in basic or acid medium under conditions identical with those described above for the hydrolysis of a nitrile, followed by a period of heating in acid medium in order to decarboxylate the intermediate α-di-acid obtained.

i) The conversion of other precursor groups of the carboxylic acid group into a carboxylic group by oxidation.

This conversion concerns especially the intermediates II in which Z represents a group such as $—CH_2OH$; $—CHO$: $—CHOH—CH_3$; $—CO—CH_3$; $—CH_2—CHOH—CH_3$; $—CH_2—CO—CH_3$, $—CH{=}CH—R_4$ and $—CHOH—CHOH—R_4$ in which R_4 possesses the values defined above. It is carried out conventionally by the expedient of a large number of oxidation agents and in accordance with a great diversity of well known processes.

The oxidation proceeds by way of several intermediate products which can be isolated in certain cases and according to the nature of the oxidation agent it is carried out in water or in an organic inert solvent.

Of course the selection of the oxidation agent and of the reaction conditions will take place as a

function of the nature of the group Z and in such manner as to maintain intact the other groups present in the molecule II.

j) The transformation of an acid into ester and *vice versa*. The esterification of an acid is a very general reaction which can be produced in many ways. Classically, acid and alcohol are placed in reaction in the presence of an acid catalyst. This reaction is advantageously carried out under anhydrous conditions and one of the reactants is used in great excess. The solvent can be either one of the reactants or an inert organic solvent.

Another manner of proceeding consists in distilling the water as soon as it is formed, utilising an appropriate apparatus. The reaction conditions are identical with those described, with the exception of the fact that one of the reactants must not be engaged in great excess.

The hydrolysis of the ester takes place in conditions of acid or basic catalysis but in this case one of the reactants, in the present case the water, is used in very great excess.

k) The conversion of the group Z representing an alkoxycarbonyl group (—COOR'), a carboxylic group, its salt or its anion into an alkoxycarbonyl group (—$COOR_3$).

According to the nature of Z this conversion can be effected by esterification, as described in the previous paragraph, by transesterification, by heating the derivative II containing the group —COOR' in the presence of an excess of alcohol R_3OH and an acid or basic catalyst, advantageously continuously eliminating the formed alcohol R'OH by distillation, or by alkylation by means of the reactant WR_3, where W represents an easily substitutable group like a halogen such as chlorine, bromine or iodine, an O-mesyl or O-tosyl group, a sulphate group (—O—SO_2—OR_3), an acyl oxy group (R_5—CO—O) or a hydroxyl group. R_3 represents a linear or branched alkyl group C_1—C_3 and R_5 represents a group R_3 or phenyl. The alkylation of the carboxylic group, its salt or its anion takes place normally in an inert organic solvent in the presence of a weak inorganic base or preferably of an organic base such as pyridine or triethylamine.

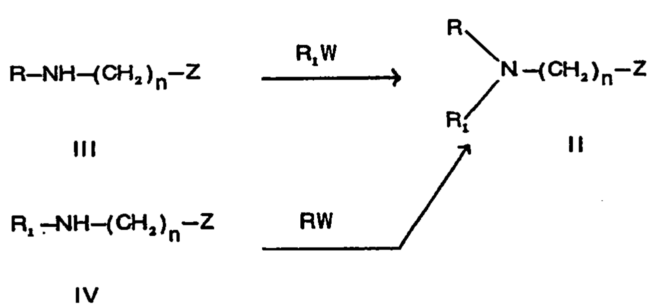
l) The conversion of Z, representing an atom of halogen, into a carboxylic acid group.

This conversion is carried out classically by transforming the halogenated product into an organometallic derivative, the carbon dioxide treatment of which, followed by hydrolysis of the intermediate form, supplies the carboxylic group. The metal utilised can be lithium, magnesium, zinc or manganese.

In order to avoid secondary reactions in this conversion, the functional group RR_1N— present in the molecule II will be adequately protected.

For better understanding of the process the principle ways of access to the derivative II will be described below:—

1. The derivative II can be obtained at the expense of the products III or IV by alkylation or acylation according to the following outlines.



wherein

R, R_1, Z, W and n possess the values as defined above, but in the reactant R_1W the group R_1 does not represent hydrogen. RW and R_1W can likewise represent a cetene of formula

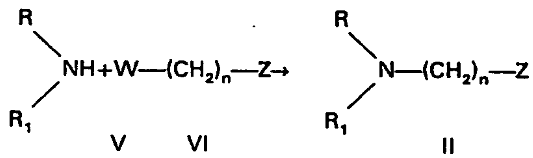
$$\begin{matrix}R_6 \\ & \diagdown \\ & & C{=}C{=}O \\ & \diagup \\ R_7\end{matrix}\text{, so that the group }\begin{matrix}R_6 \\ & \diagdown \\ & & CH{-}CO\text{,} \\ & \diagup \\ R_7\end{matrix}$$

obtained after the acylation of the derivatives III or IV, corresponds according to the case to a group R or R_1. This alkylation or acylation reaction can be effected in an inert organic solvent such as a chlorinated hydrocarbide, an alcohol or an aliphatic or aromatic hydrocarbide, selected as a function of the nature of the reactant.

The reaction proceeds at a temperature between 0°C and the reflux temperature of the solvent. The reaction can advantageously be carried out in the presence of organic base such as trimethyl amine,

pyridine or N-dimethylaniline or of mineral base such as the hydroxides, the carbonates and the bicarbonates of alkaline or earth-alkaline metals or finely pulverised lime.

A variant of this process is illustrated below:—



V VI II

R, R_1, W, Z and n possess the values defined previously.

The above reaction is similar to the alkylation reaction of the derivatives III or IV described above, and of course the operating conditions for these three reactions are entirely comparable.

According to another variant of the process, the derivative II can be synthesised by acylation from a primary amine by a carboxylic acid making use of phosgene as coupling agent. The phosgene can be introduced in a solution of the amine and carboxylic acid or it can be opposed to one of the two reactants and the intermediate thus formed is then opposed to the second reactant.

This variation in which the phosgene is set into reaction with the amine IV, followed by the transformation of the intermediate isocyanate, is illustrated by the following diagram:—

$$R_1NH\text{—}(CH_2)_n\text{—}Z \xrightarrow{COCl_2} O{=}C{=}N\text{—}(CH_2)_n\text{—}Z$$

IV

$$\xrightarrow{R_8\text{—}COOH} R_8\text{—}CO\text{—}\underset{\displaystyle R_1}{\underset{|}{N}}\text{—}(CH_2)_n\text{—}Z$$

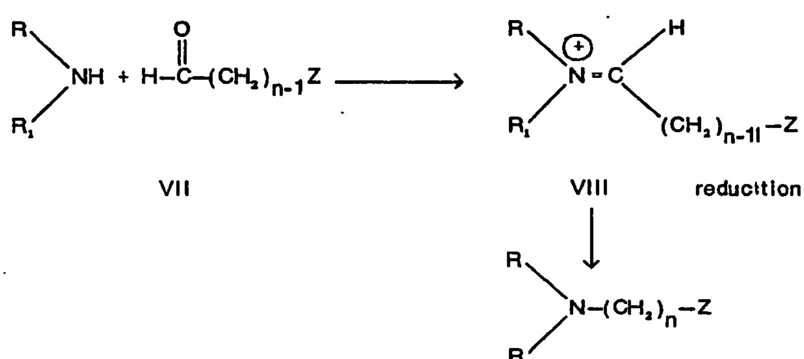
wherein

R_1 represents hydrogen, Z and n possess the values specified previously and the group R_8—CO corresponds to the group R as defined previously.

According to another variant the derivative II in which R represents an alkyl or substituted alkyl group as defined above can be obtained by acylation of the derivatives III or IV, as described above, followed by a reduction of the amide obtained as intermediate. Numerous methods are described for effecting such a reduction, but it is apparent that the selection of the reaction conditions must include ensuring the preservation of the functionality of the group Z.

2. Another way of access to the derivative II is characterised by the formation of an intermediate iminium salt VIII at first from an amine and a carbonyl compound VII.

The reduction of the iminium salt leads to derivative II.

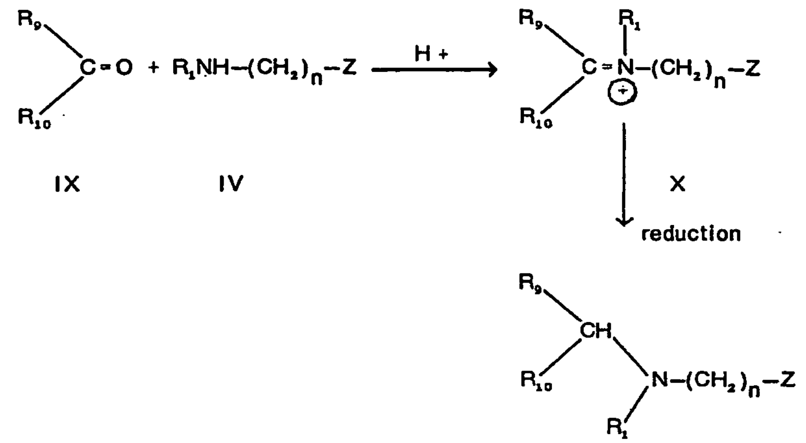


VII VIII reduction II

The condensation between the amine and the carbonyl derivative VII takes place conventionally in an inert organic solvent, preferably not miscible with water. The reaction is advantageously catalysed by a mineral or organic acid.

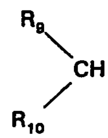
The reduction takes place in an appropriate solvent in conventional manner by means of hydrogen in the presence of a hydrogenation catalyst, by means of an alkali metal hydride, by aluminium and

lithium hydride or at least one other reduction agent, but of course the method of reduction of the iminium salt will be selected so as to keep intact the functionality of the group Z. By selecting the reactants differently it is possible to realise a variant of this process which permits of arriving at the product II passing by way of intermediate carrying the same chemical functions as above.



IX IV X

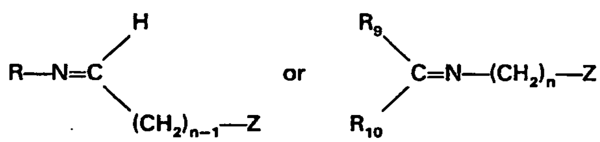
R_1, Z and n possess the meanings given previously while the groups R_9 and R_{10} possess values such that the group



is equivalent to R.

The condensation of the carbonyl derivative with the amine IV and the reduction of the iminium salt X take place under the conditions described above.

It should be remarked that when R_1 represents hydrogen, the above-described condensations lead to an imine of formula:

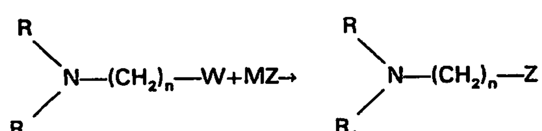


XI XII

wherein

R, R_9, R_{10}, Z and n have the values defined above. The conditions of synthesis and reduction of the imines XI and XII are completely comparable with those of the synthesis and reduction of the iminium salts VIII and X.

3. Another way of access to the derivatives of formula II consists in the transformation of a product of formula XIII by the expedient of reactant XIV, according to the following diagram:—



XIII XIV II

R, R_1, W and n have the meanings given above, M represents hydrogen or a metal such as lithium, sodium potassium or magnesium and Z has the values given above compatible with a reaction envisaged above, such that: a nitrile group, a trihalomethyl group or a cyclic of noncyclic dithioacetal group.

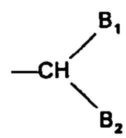
The transformation of the product XIII can be realised in accordance with different conventional methods selected as a function of the nature of W and Z. Certain of these methods are summarised here by way of example:—

a) when Z represents a nitrile or trihalomethyl group, the reaction can be carried out in different solvents such for example as water, a lower alcohol, dimethyl formamide or in mixtures of solvents, miscible or not.

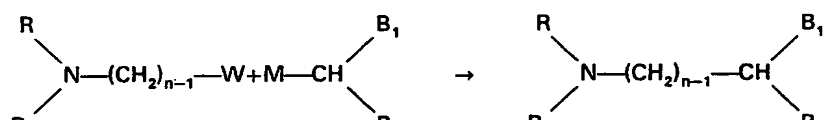
In several cases it is advantageous to work in the presence of an organic base or a phase transfer catalyst.

b) when Z represents a cyclic or non-cyclic dithioacetal group, the reaction occurs under anhydrous, low-temperature conditions, in an inert solvent such as diethyl ether or tetrahydrofuran. Then the product II is obtained by deprotection of the formyl group by well-known methods such as hydrolysis in acid medium or by the action of mercury salts.

4. Another way of access to derivatives of formula II in which —CH_2Z represents the group



consists in the alkylation of a derivative XV by means of the reactant XVI according to the following diagram:—



XV XVI

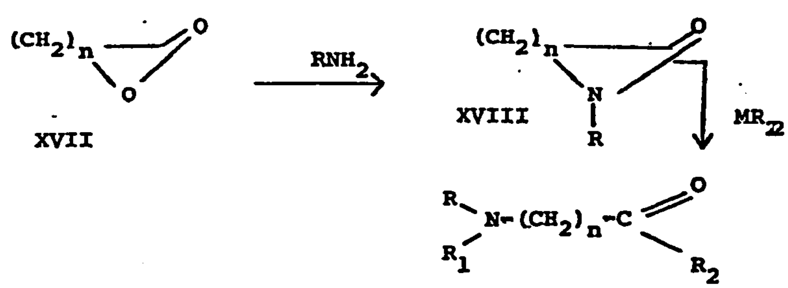
R, R_1, B_1, B_2, W and n have the values given previously, with the exception of W which, in this case, does not represent a hydroxyl group.

M represents an alkaline metal such as sodium, potassium or lithium.

This conventional reaction generally occurs under inert atmosphere and anhydrous conditions, utilising a solvent such as an alcohol or an aliphatic or aromatic hydrocarbide.

Process B.

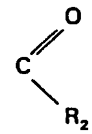
This process consists in the opening of a lactam XVIII, under the action of a base or an acid. The said lactam XVIII is conventionally obtained from the lactone XVII according to the diagram:—



XVII XVIII I (R_1=H)

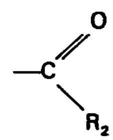
R, R_2, M and n have the values defined above. The conversion of the lactone into lactam takes place in an inert organic solvent, advantageously at the reflux temperature of the reaction medium. The opening of the lactam can take place under the action of ammonia, an amide, an alcoholate or a hydroxide of an alkali metal, or under the action of a mineral acid such as hydrochloric acid or sulphuric acid. It proceeds in water or in an inert organic solvent such as an ether, an alcohol, an aliphatic hydrocarbide or aromatic hydrocarbide or a chlorinated hydrocarbide.

It is apparent that the methods described for the synthesis of the compound II can apply equally to products in which the group Z already possesses the value of the group



as specified previously and thus can lead directly to the products of the invention corresponding to the general formula I.

Of course for all the processes of synthesis of the compounds of formulas I and II, and for those cited for the transformation of group Z and CH_2—Z into a group



the reactants and reaction conditions are selected so as to keep intact the functional groups already present in the molecule and not involved in the envisaged reaction.

Thus in order to be able to carry out the synthesis of the compounds I and II it is sometimes necessary to utilise protective groups in order to preserve the functionality of the groups present in the initial molecule. The selection of the experimental conditions will contain the selection of the protective groups which, like the processes for their introduction and the methods of deprotection, are clearly described in literature.

Some detailed examples of preparation of several derivatives according to the invention are given below.

These examples are primarily for the purpose of further illustrating the particular characteristics of the processes according to the invention.

EXAMPLE 1

Synthesis of 4-n-pentylamino butanamide

5 g. (0.041 m.) of 4-chlorobutanamide are dissolved in 19 ml. (0.165 m.) of pentanamine and agitated for 48 hours at ambient temperature. By addition of ether (400 ml.) a precipitate forms which is filtered and recrystallised twice in isopropanol.

M (°C):187

Elementary analysis:

	C	H	N
% calculated	51.7	10.1	13.4
% found	52.0	10.2	13.4

EXAMPLE 2

Synthesis of 5-n-pentylaminopentanamide

a) A mixture of 4.5 g. of 5-chloropentane nitrile (0.040 m.), 3.8 g. (0.044 m.) of pentanamine, 3.7 g. of sodium bicarbonate in 60 ml. of absolute ethanol is brought to reflux for 48 hours. The formed sodium chloride is filtered and the filtrate is evaporated to dryness *in vacuo* to eliminate the excess pentanamine. The residual oil is dissolved in ether and ether/HCl is added. A white precipitate forms which is filtered (5-n-pentylamino-pentanenitrile hydrochloride).

M (°C):207—209.

b) 2.78 g. (0.013 m.) of 5-n-pentylamino pentanenitrile hydrochloride are suspended in 3.4 ml. of concentrated HCl and agitated at 5°C. for 6 days. The limpid solution obtained is poured over 20 ml. of isopropanol, the solid which crystallises is filtered and washed with isopropanol.

M. (°C):216—217.

Elementary analysis:

	C	H	N
% calculated	53.9	10.4	12.5
% found	54.2	10.5	12.6

EXAMPLE 3

Synthesis of 6-decylaminohexanamide

4.5 g. of 6-chlorohexanamide (0.030 m.) are heated under reflux in 100 ml. of ethanol containing 5.2 g. of decanamine (0.033 m.) and 2.52 g. of $NaHCO_3$ (0.033 m.). After 2 days and 2 nights the solution is cooled, filtered and evaporated; the solid is recrystallised twice in ethyl acetate. The solid

obtained is dissolved in ethanol and ether/HCl is added; the new solid obtained is recrystallised twice in isopropanol.
M. (°C.):206
Elementary analysis:

	C	H	N
% calculated	62.6	11.5	9.1
% found	63.0	11.7	9.3

EXAMPLE 4
Synthesis of 5-(p.tolyl acetylamino) pentanamide

2.9 g. (0.017 m.) of p-tolylacetyl chloride and a solution of 0.7 g. of NaOH in 4 ml. of water are added drop by drop simultaneously to a solution of 0.7 g. (0.017 m.) of NaOH and 2 g.. of 5-aminopantanamide (0.017 m.) in 10 ml. of water cooled to 0°C. The suspension which has formed is agitated for one hour at room temperature. The solid is filtered and recrystallised twice in isopropanol.
M. (°C.):206
Elementary analysis:

	C	H	N
% calculated	67.7	8.1	11.3
% found	67.8	8.1	11.3

EXAMPLE 5
Synthesis of 4-pentylamino butanoic acid

7.75 g. of pentanal (0.090 m.), 7.73 g. of gamma aminobutanoic acid (0.075 m.)), 800 mg. of palladium at 10% over carbon, 5 g. of 3 Å molecular screen and 200 ml. of absolute ethanol are introduced into a Parr bottle. The bottle is agitated under an atmosphere of hydrogen for 18 hours. The suspension is filtered and the filtrate evaporated to dryness at 20°C. under reduced pressure. The solid is washed with ether, dissolved in the minimum of ethanol and ether is added. The crystals obtained are recrystallised once again in the same manner.
M (°C.):161—162
Elementary analysis:

	C	H	N
% calculated	62.4	11.0	8.1
% found	62.1	11.1	8.0

EXAMPLE 6
Synthesis of 6-(3-(3,4-dimethoxyphenyl)propanylamino)hexanamide

4.6 g. (0.02 m.) of 3-(3,4-dimethoxyphenyl)propanyl chloride and 2.4 g. of NaOH in 20 ml of water are added simultaneously to a solution of 2.6 g. (0.020 m.) of 6-aminohexanamide and 0.8 g. of NaOH in 15 ml. of water, cooled to 0°C. The suspension is agitated for two hours at room temperature. Then the solid is filtered and recrystallised in isopropanol.
M (°C.):137
Elementary analysis

	C	H	N
% calculated	63.3	8.1	8.7
% found	63.2	8.2	8.6

EXAMPLE 7
Synthesis of 6-n-pentylaminohexanamide

A mixture of 5 g. of 6-chlorohexanamide (0.033 m.), 4.25 ml. of pentanamine (0.037 m.) and 2.8 g. of sodium bicarbonate (0.034 m.) in 100 ml. of ethanol is heated under the reflux for four days. Then after cooling of the solution the salts are filtered and the solvents are evaporated to dryness. The solidifying product is crystallised twice in ethyl acetate, dissolved in a minimum of methanol and ether/HCl is added. The solid forming is filtered and dried.
M (°C.):190.5
Elementary analysis:

	C	H	N
% calculated	55.8	10.6	11.8
% found	55.8	10.6	11.8

EXAMPLE 8

Synthesis of 4-n-hexylaminobutanamide

a) A mixture of 18.5 ml. of 4-chlorobutanenitrile (0.2 m.), 29.1 ml. of hexanamine (0.22 m.) and 18.5 g. of sodium bicarbonate (0.22 m.) in 500 ml. of ethanol is heated under reflux for two days. Then the suspension is cooled, the salts are filtered and the filtrate is evaporated. The residue is shared between water and dichloromethane. The dichloromethane phase is washed with water, dried over K_2CO_3 and evaporated at room temperature. The excess of hexanamine is evaporated under high vacuum and the residual oil is dissolved in anhydrous ether and ether/HCl is added. The solid appearing is filtered, dissolved in a minimum of methanol and anhydrous ether is added. The product thus obtained is engaged as such in the following stage.

b) 4.2 g. of 4-hexylaminobutanenitrile (0.02 m.) are agitated for four days at 5°C in 5 ml. of concentrated HCl. Then this solution is poured into 50 ml. of chilled acetone. The white solid which forms is recrystallised in isopropanol.

M (°C.):194

Elementary analysis:

	C	H	N
% calculated	53.9	10.4	12.6
% found	54.1	10.4	12.6

EXAMPLE 9

Synthesis of 4-[(N-n-hexyl-N-4-chlorophenylacetyl)amino]butanamide

650 mg. of 4-hexyhlaminobutanamide hydrochloride (0.003 m.) are dissolved in 9.4 ml. of KOH 1 N at 10°C. To this solution 0.65 ml. of 4-chlorophenyl acetic acid chloride are added drop by drop. An oil appears immediately and solidifies. After two hours of reaction the oil is extracted with ether, the ethereal phase is washed with water and 1 N hydrochloric acid, it is dried over K_2CO_3 and evaporated. The residual solid is recrystallised in ethyl acetate.

M (°C).:105—106

Elementary analysis:

	C	H	N
% calculated*	63.1	8.0	8.2
% found	63.0	7.9	8.1

*calculated for a content of 1.03% H_2O.

EXAMPLE 10

Synthesis of 5-n-dodecylaminopentanamide

a) 7.4 g. of dodecanamine (0.04 m.), 4.23 g. of 5-chloropentanenitrile (0.036 m.) and 3.4 g. of sodium bicarbonate (0.04 m.) in 100 ml. of ethanol are heated under reflux for two days. Then the cooled solution is filtered and the filtrate evaporated. The residual oil is distilled under 0.25 mm of Hg. The fraction distilling at 170°C. is collected. It is dissolved in ethanol and ether/HCl is added. The solid precipitating is filtered and used without supplementary purification in the following stage.

b) 2 g. of 5-dodecylaminopentanenitrile hydrochloride (0.007 m.) are dissolved in 50 ml. of acetic acid. This solution is saturated with dry hydrochloric acid and agitated at room temperature for two days. The acetic acid is then evaporated, the solid taken up in ether is filtered and the solid recrystallised twice in isopropanol.

M (°C.):212

Elementary analysis:

	C	H	N
% calculated	63.6	11.6	8.7
% found	63.9	11.6	8.8

EXAMPLE 11

Synthesis of 4-n.pentylaminobutanamide

a) A mixture of 18.5 ml. of 4-chlorobutanenitrile (0.2 m.), 19.1 g. of pentanamine (0.22 m.) and 18.5 g of sodium bicarbonate (0.22 m.) in 500 ml. of ethanol is heated under reflux for 2 days. Then the suspension is cooled, the salts are filtered and the filtrate is evaporated. The residue is shared between water and dichloromethane. The dichloromethane phase is washed with water, dried over K_2CO_3 and evaporated at room temperature. The excess of pentanamine is evaporated under high vacuum and the residual oil is dissolved in anhydrous ether and ether/HCl is added. The solid appearing is filtered, dissolving in a minimum of methanol and anhydrous ether is added until an abundant precipitate is obtained which is filtered and engaged as such in the following stage.

b) 3.1 g. of 4-pentylaminobutanenitrile (0.02 m.) are dissolved in 30 ml. of glacial acetic acid and are saturated with HCl at room temperature.

After agitation for 24 hours, the acetic acid is evaporated and the residual solid is recrystallised in isopropanol.
M (°C.):187.5
Elementary analysis:

	C	H	N
% calculated	51.7	10.1	13.4
% found	51.8	10.2	13.4

EXAMPLE 12
Synthesis of 4-n.pentylaminobutanamide

2.76 g. of 4-aminobutanamide hydrochloride (0.02 m.), 1.9 g. of pentanal (0.022 m.), 100 mg. of Pd/C at 10% and 50 ml. of ethanol are introduced into a Parr bottle. The bottle is agitated for one night under an atmosphere of hydrogen at ambient temperature. The catalyst is then filtered, the solvent evaporated and the residue solidified in ether. The solid obtained is recrystallised three times in isopropanol.
M (°C.):186.5
Elementary analysis:

	C	H	N
% calculated	51.7	10.1	13.4
% found	52.0	10.3	13.5

EXAMPLE 13
Synthesis of 4-n. pentylaminobutanamide

3.1 g. of N-pentylpyrrolidone (0.02 m.) are introduced into a 200 ml. flask containing 3.9 g. of sodium amide (0.1 m.) suspended in 50 ml. of toluene. The suspension is brought to reflux for 3 hours, after which there are added 10 ml. of H_2O and sufficient HCl 1 N to render the solution acid (pH 2). The aqueous phase is decanted and lyophilised. The residue is extracted with boiling isopropanol, the solid which crystallises is filtered and recrystallised twice in isopropanol.
M (°C.):186
Elementary analysis:

	C	H	N
% calculated	51.7	10.1	13.4
% found	51.4	10.0	13.7

EXAMPLE 14
Synthesis of 4-(2-phenylethylamino) butanoic acid

a) 500 ml. of toluene and 15.2 ml. of pyrrolidone (0.2 m.) are introduced under nitrogen into a 1 litre flask cooled in an ice bath. 9.6 g. of sodium hydride (0.4 m.) are added in three stages to this solution. After stirring for one hour at 0°C, the suspension is allowed to return to room temperature. 37.15 ml. of 2-phenyl-1-bromoethane (0.27 m.) are then added and the whole amount is brought to reflux for 12 hours. After adding 100 ml of water, the toluene phase is decanted and washed three times with water, dried over K_2CO_3 and evaporated; the residual oil is distilled under 10 mm Hg. The colourless liquid is collected which distills at 175°C and which is identified as N-(2-phenylethyl)pyrrolidone.

b) 17.9 g. of n-(2-phenylethyl)pyrrolidone (0.095 m.) are brought to reflux in 25 ml. of concentrated HCl for 20 hours. The solution is then evaporated to dryness and the solid residue is crystallised in methylethyl ketone.
M (°C.):149—150
Elementary analysis:

	C	H	N
% calculated	59.1	7.4	5.8
% found	59.2	7.5	5.7

EXAMPLE 15
Synthesis of the ethyl ester of 4-(2-phenylethylamino)butanoic acid

1 g. of the hydrochloride of 4-(2-phenylethylamino) butanoic acid (0.004 m.) is brought to reflux for 1 hour in 10 ml. of ethanol/HCl 5N. The solution is then evaporated to dryness and the solid obtained is recrystallised in methylethyl ketone.
M (°C.):206—207

Elementary analysis

	C	H	N
% calculated	61.9	8.2	5.1
% found	61.9	8.2	5.2

Table I given below assembles the derivatives of the above examples and also other derivatives of the invention prepared in accordance with the above processes. All the compounds assembled in Table I give a correct C.H.N. elementary analysis.

TABLE I

$$R - \underset{\displaystyle R_1}{\underset{|}{N}} - (CH_2)_n - C \overset{\displaystyle O}{\diagup\!\!\diagup} \diagdown R_2$$

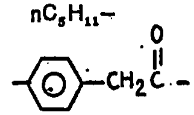
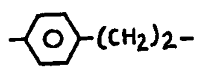
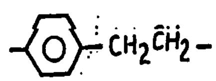
CP Code	No	R	R_1	R_2	n	M(°C) B.p.(°C)/mb	Recrystallisation Solvent
2081	1	$nC_5H_{11}-$	H	NH_2	3	187–188	Isopropanol (1)
2455	2		H	NH_2	3	164–166	Isopropanol
2624	3		H	NH_2	3	188–189	Isopropanol (1)
2631	4	$nC_8H_{17}-$	H	NH_2	3	195–196	Isopropanol (1)
2632	5	$nC_5H_{11}-$	H	NH_2	4	216–217	Isopropanol (1)
2633	6	$nC_6H_{13}-$	H	NH_2	3	193–194	Isopropanol (1)
2657	7		H	NH_2	4	214–215	EtOH (1)
2659	8	$nC_5H_{11}-$	H	NH_2	5	190–191	MeOH–Ether

TABLE I

$$R-\underset{\displaystyle R_1}{\underset{|}{N}}-(CH_2)_n-C\overset{\displaystyle O}{\underset{\displaystyle R_2}{\lessgtr}}$$

CP Code	No	R	R_1	R_2	n	M(°C) B.P.(°C)/mb	Recrystallisation Solvent
2678	9	$nC_6H_{13}-$	$C_6H_5-CH_2-CO-$	NH_2	3	76–78	Benzene-pentane
2679	10	$Cl-C_6H_4-O(CH_2)_2-$	H	NH_2	5	193	Isopropanol (1)
2681	11	$CH_3-C_6H_4-(CH_2)_4-$	H	NH_2	5	196	Isopropanol (1)
2685	12	$C_6H_5-(CH_2)_4-$	H	NH_2	3	179–180	Isopropanol (1)
2711	13	$nC_6H_{13}-$	$Cl-C_6H_4-CH_2-CO-$	NH_2	3	105–106	AcOEt
2684	14	$C_6H_5-(CH_2)_4-$	$CH_3-C_6H_4-CH_2-CO-$	NH_2	3	88–89	AcOEt
2728	15	$C_6H_5-(CH_2)_2-$	H	NH_2	5	195	EtOH (1)

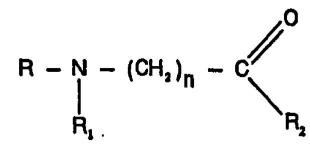
19

TABLE I

$$R - \underset{\displaystyle R_1}{\underset{|}{N}} - (CH_2)_n - C(=O) - R_2$$

CP Code	No	R	R_1	R_2	n	M(°C) B.P.(°C)/mb	Recrystallisation Solvent
2818	16	$nC_5H_{11}-$	H	OH	3	161–162	EtOH–Ether
2982	17	$n.C_4H_9-$	H	NH_2	5	184	EtOH (1)
2983	18	$n.C_9H_{19}-$	H	NH_2	5	205	MeOH–Ether (1)
2984	19	$C_6H_5-O-(CH_2)_4-$	H	NH_2	5	169	EtOH (1)
3002	20	$n.C_{10}H_{21}-$	H	NH_2	5	206	EtOH (1)
3003	21	$n.C_7H_{15}-$	H	NH_2	5	201	Isopropanol (1)
3027	22	$C_6H_5-CH_2-CH(CH_3)-$	H	NH_2	5	$170°/2.10^{-3}$	–
3028	23	$n.C_4H_9-CH(C_2H_5)-$	H	NH_2	5	$180°/8.20^{-4}$	–
3045	24	$n.C_{11}H_{23}-$	H	NH_2	4	212	AcOH (1)

TABLE I



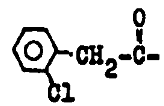
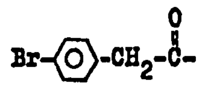
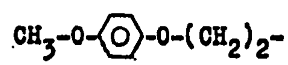
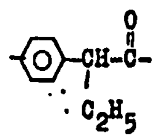
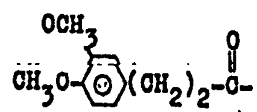
CP Code	No	R	R_1	R_2	n	M(°C) B.P.(°C)/mb	Recrystallisation Solvent
3063	25		H	NH_2	5	142	Isopropanol
3064	26		H	NH_2	5	149	Isopropanol
3065	27		H	NH_2	4	204	MeOH (1)
3073	28		H	NH_2	5	109.6	Isopropanol
3074	29		H	NH_2	5	137	Isopropanol
3075	30	n.$C_{12}H_{25}$–	H	NH_2	4	212	Isopropanol (1)

TABLE I

$$R-\underset{\underset{R_1}{|}}{N}-(CH_2)_n-C\!\begin{smallmatrix}\nearrow O \\ \searrow R_2\end{smallmatrix}$$

CP Code	No	R	R_1	R_2	n	M(°C) B.P.(°C)/mb	Recrystallisation Solvent
3076	31	$CH_3-C_6H_4-CH_2-\overset{O}{\overset{\Vert}{C}}$	H	NH_2	4	206	Isopropanol
3077	32	$n.C_5H_{11}-$	$-C_6H_4-\underset{C_2H_5}{\underset{\vert}{CH}}-\overset{O}{\overset{\Vert}{C}}-$	NH_2	4	$250/3.10^{-3}$	–
3078	33	CH_3-CH_2-	H	NH_2	4	166	Isopropanol
3087	34	$n.C_5H_{11}-$	$CH_3-C_6H_4-CH_2-\overset{O}{\overset{\Vert}{C}}-$	NH_2	4	$270/3.10^{-3}$	–
3088	35	$n.C_5H_{11}-$	$Br-C_6H_4-CH_2-\overset{O}{\overset{\Vert}{C}}-$	NH_2	4	75	AcOEt
3089	36	$(CH_3O)(CH_3O)C_6H_3-CH_2-CH_2-$	H	NH_2	4	192	EtOH–Ether (1)
3112	37	$n.C_5H_{11}-$	$n.C_9H_{19}-\overset{O}{\overset{\Vert}{C}}-$	NH_2	4	$240/10^{-3}$	–

TABLE I

$$R-\underset{\displaystyle R_1}{N}-(CH_2)_n-C\overset{\displaystyle O}{\lessgtr}{}_{R_2}$$

CP Code	No.	R	R_1	R_2	n	M(°C) B.P.(°C)/mb	Recrystallisation Solvent
3113	38	$n.C_5H_{11}-$	$(C_3H_7)_2CH-C(=O)-$	NH_2	4	$190/10^{-3}$	-
3114	39	$n.C_5H_{11}-$	$C_4H_9-C(=O)-$	NH_2	4	$240/10^{-3}$	-
3115	40	$(CH_3)_2CH-$	H	NH_2	4	151	MeOH-Ether (1)
3116	41	$n.C_5H_{11}-$	$Cl-C_6H_4-CH_2-C(=O)-$	NH_2	4	90	AcOEt-Pentane
3117	42	$n.C_5H_{11}-$	$CH_3O-C_6H_4-CH_2-C(=O)-$	NH_2	4	77	AcOEt
3124	43	$F-C_6H_4-CH_2-C(=O)-$	H	NH_2	4	182	Isopropanol
3125	44	$n.C_5H_{11}-$	H	OH	4	130	Methylethylketone(1)

TABLE I

$$R-\underset{R_1}{N}-(CH_2)_n-C\begin{smallmatrix}\nearrow O\\ \searrow R_2\end{smallmatrix}$$

CP Code	No.	R	R_1	R_2	n	M(°C) B.P.(°C)/mb	Recrystallisation Solvent
3128	45	$Cl-C_6H_4-CH_2-C(=O)-$	H	OH	4	118	AcOEt
3147	46	$C_6H_5-CH_2-CH_2-$	H	OH	3	149	Methylethylketone (1)
3148	47	$CH_3O-C_6H_4-(CH_2)_3-C(=O)-$	H	NH_2	3	151.5	AcOEt-Isopropanol
3149	48	$C_6H_5-(CH_2)_2-C(=O)-$	H	NH_2	3	140.9	AcOEt
3150	49	$Cl-C_6H_4-CH_2-C(=O)-$	H	NH_2	4	197	Isopropanol
3151	50	$C_6H_5-CH(C_2H_5)-C(=O)-$	H	OC_2H_5	3	$160/2.10^{-3}$	
3152	51	$C_6H_5-CH(C_2H_5)-C(=O)-$	H	OCH_3	3	$160/3.10^{-3}$	

TABLE I

$$R-\underset{R_1}{N}-(CH_2)_n-C\overset{O}{\underset{R_2}{<}}$$

CP Code	No.	R	R_1	R_2	n	M(°C) B.P.(°C)/mb	Recrystallisation Solvent
3153	52	$C_6H_5-CH(C_2H_5)-CO-$	H	NH_2	3	109.6	AcOEt
3154	53	$C_6H_5-CH(C_2H_5)-CO-$	H	OH	3	85	AcOEt
3155	54	$C_6H_5-(CH_2)_4-CO-$	H	NH_2	5	122	Isopropanol
3156	55	$n.C_5H_{11}-$	CH_3-CO-	NH_2	4	$200/2.10^{-3}$	
3157	56	$C_6H_5-(CH_2)_2-$	$C_6H_5-(CH_2)_3-CO-$	OH	3	$150/10^{-3}$	
3158	57	$n.C_5H_{11}-$	H	OH	5	94-95	Methylethylketone(1)
3159	58	$C_6H_5-(CH_2)_2-CO-$	H	OH	3	63	$MeOH-H_2O$

TABLE I

$$R - \underset{R_1}{N} - (CH_2)_n - C(=O)R_2$$

CP Code	No.	R	R_1	R_2	n	M(°C) B.P.(°C)/mb	Recrystallisation Solvent
3160	59	$C_6H_5-(CH_2)_4-C(=O)-$	H	OCH_3	3	$180/2.10^{-3}$	
3161	60	$C_6H_5-(CH_2)_4-C(=O)-$	H	NH_2	3	128	AcOEt
3162	61	$CH_3-O-C_6H_4-(CH_2)_3-C(=O)-$	H	OH	3	81	AcOEt
3163	62	$C_6H_5-(CH_2)_3-$	$(C_3H_7)_2CH-C(=O)-$	OH	5	$250/3.10^{-3}$	
3164	63	$C_6H_5-(CH_2)_3-$	H	OC_2H_5	5	156-158	Acetone-Ether (1)
3165	64	$C_6H_5-(CH_2)_2-$	H	OCH_3	3	217-218	MeOH

TABLE I

$$R - \underset{R_1}{N} - (CH_2)_n - C \begin{matrix} {}^{\nearrow O} \\ {}_{\searrow R_2} \end{matrix}$$

CP Code	No.	R	R_1	R_2	n	M(°C) B.P.(°C)/mb	Recrystallisation Solvent
3166	65	$C_6H_5-(CH_2)_2-$	H	OC_2H_5	3	206-207	Methylethylketone (1)
3167	66	$C_6H_5-(CH_2)_3-$	H	OH	5	119-120	Acetonitrile (1)
3168	67	$C_6H_5-(CH_2)_2-C(=O)-$	H	OC_2H_5	3	$170/10^{-1}$	
3169	68	$C_6H_5-(CH_2)_2-C(=O)-$	H	$O-CH(CH_3)_2$	3	$175/10^{-1}$	
3170	69	$Cl-C_6H_4-CH_2-C(=O)-$	H	$O-C_2H_5$	4	108	Toluene-Heptane
3171	70	$C_6H_5-CH(C_2H_5)-C(=O)-$	H	$O-CH(CH_3)_2$	3	$168/10^{-1}$	
3173	71	$C_6H_5-(CH_2)_4-C(=O)-$	H	$O-CH(CH_3)_2$	3	$200/10^{-1}$	

TABLE I

$$R-\underset{R_1}{N}-(CH_2)_n-C\overset{O}{\ }\!\!\diagdown R_2$$

CP Code	No.	R	R_1	R_2	n	M(°C) B.P.(°C)/mb	Recrystallisation Solvent
3174	72	$C_6H_5-(CH_2)_3-$	H	OCH_3	5	169-170	Acetone-Ether (1)
3175	73	$C_6H_5-(CH_2)_3-$	$(C_3H_7)_2CH-\overset{O}{\overset{\parallel}{C}}-$	OC_2H_5	5	$200/2.10^{-3}$	

(1) hydrochloride

The products according to the invention were subjected to a series of pharmacologicall tests the methodology of which is described below.

The LD_{50}s are calculated according to the method of Lichtfield and Wilcoxon (J. Pharmacol. Exp. Ther. *96,* 99, 1949) and expressed in mg/kg. The products were administered orally to mice. In general the products of the invention revealed themselves of low toxicity. The effect upon the behaviour is studied utilising a method derived from that of S. Irwin (Gordon Res. Conf. on Medicinal Chem., *133,* 1959). The substances, suspended in a mucilage 1% of gum tragacanth, are administered orally by means of an intragastric probe to groups of five male mice fasting for eighteen hours. The doses tested as a function of the observed activity go from 3,000 to 3 mg/kg.

The behaviour is studied 2, 4, 6 and 24 hours after treatment. The observation is prolonged if symptoms persist at this time. The mortalities were registered in the course of 14 days following the treatment. None of the products tested has induced any abnormal behaviour in the mouse.

The numbers refer to the numbers given to the products in column 2 of Table I.

In general certain products of the invention are endowed with an anti-convulsive activity. The anti-convulsive activity is examined in relation to tonic convulsions induced by bicuculline. The compounds according to the invention were administered orally at the dosage of 10 mg/kg to 20 mice, three hours before the intravenous injection of bicuculline, at the dose of 0.7 mg/kg. The number of mice protected against tonic convulsions and death is noted.

In this test products Nos. 1, 5, 8, 10 and 13 were revealed to be particularly active and give a protection percentage equal to or greater than 55%.

CP 2081 (compound No. 1 in Table I) was the subject of a more profound evaluation. In the test of inhibition of convulsions induced by bicuculline, the LD_{50} is 3 mg/kg. At the dose of 300 mg/kg. the percentage of protection against convulsions induced by bicuculline is 75%.

CP 2081 likewise possesses an effect opposing convulsions induced by leptazole and by electric shocks.

Biochemical tests have demonstrated that certain products of the invention possess a GABA-mimetric derived from that of C. Braestrup and M. Nielsen (Brain Research Bulletin, Vol. 5, suppl. 2, p. 681—684 (1980)).

A homogenate of rat brain (without cerebellum) washed in order to eliminate the GABA (γ-aminobutanoic acid) present, is utilised to measure the connection to the receiver (the "binding") by means of ^{3}H-flunitrazepam in the presence and absence of increasing concentrations of the products to be tested or of a reference product (in the present case GABA).

The non-specific "binding" is determined in the presence of Diazepam.

The incubation takes place for 60 minutes at 0°C., on a homogenate diluted 200 times. After incubation the samples are filtered and washed over Whatman GFB filters. After dessication of the filter at 60° for 20 minutes, the residual radioactivity is measured by means of a liquid scintillator in an appropriate medium.

Under these circumstances the product CP 2818 (compound No. 16 of Table I) behaves like a GABA-mimetic, characterised by an EC_{50} ("Enhancement concentration 50%) of 4.7—10^{-5}M compared with the EC_{50} of 8.2—10^{-7}M of GABA and by an efficacity identical with that of GABA.

CP 2818 was likewise evaluated *in vitro* in the test of the connection of ^{3}H-muscimol to the synaptic membranes of rat brains. This test is specific to the GABA-ergic receivers and permits of showing an effect for or against the GABA receivers. These are directly connected to the benzodiazepine receivers.

The preparation of the synaptic membranes and the test of connection of ^{3}H-muscimol to the synaptic membranes are identical with those published by Enna, S. J. and Snyder S. H. in Brain Research *100,* 81—97 (1978).

The value of the specific connection of the ^{3}H-muscimol to the membranes is obtained by forming the difference between the connection of the ^{3}H-muscimol alone and this connection in the presence of 10 μM of GABA.

Different concentrations of CP 2818 were utilised to determine the concentration of the product necessary to inhibit 50% of the connection of the ^{3}H-muscimol to the membranes (IC_{50}). For CP 2818 an IC_{50} of 2.5×10^{-5} was obtained. The IC_{50} of GABA in this system is 2×10^{-7}M.

The effect opposing convulsions induced by bicuculline, leptazol and electric shock and the GABA-mimetic effect indicate that the compounds according to the invention possess pharmaceutical properties which render them specially indicated for the treatment of various forms of epilepsy and dyskinesias such as Parkinsons Disease. Moreover the activity of the products at the level of the central nervous system renders these compounds potentially of interest for the treatment of certain cardiovascular troubles such as hypertension and hypotension, for the treatment of psychic troubles such as depression, troubles of the memory and troubles of the sleep, also as analgesic agents.

Certain products of the invention likewise possess an anti-thelmintic activity. This activity is measured in the rat, infested with nippostrongylus brasiliensis (stage L3). The product to be tested is administered by oesophagus probe in the form of mucilage, eight days after infestation. The rats are slaughtered on the twelfth day and the enumeration of the parasites in the intestine is effected. The results obtained are expressed in percentage of efficacy in relation to a control group.

In this test the product CP 2081 (compound No. 1 of Table I) has an efficacy percentage of 91 at the dose of 50 mg/kg.

In man the compounds according to the invention will be administered orally at doses which may be from 50 mg. to 4,000 mg; by the intravenous route the doses will be from 5 mg. to 1,000 mg.

The products according to the invention can be utilised in various Galenical forms. The following examples are not limitative and concern Galenical formulations containing active product designated by the letter A. This active product can be formed by one of the following compounds:—

4-n-pentylaminobutanamide
5-n-pentylaminopentanamide
6-n-pentylaminohexanamide
4-n-pentylaminobutanoic acid
5-(p.tolylacetylamino)pentanamide
6-n-decylaminohexanamide
6-[(2-p-chlorophenoxyethyl)amino]hexanamide
4-[(N-n-hexyl-N-4-chlorophenylacetyl)amino]butanamide.

COMPOSITION EXAMPLES

1. Tablets

A	600 mg
Sta-Rx 1500 starch	80 mg
hydroxypropylmethyl cellulose	20 mg
aerosil	5 mg
magnesium stearate	15 mg

2.

A	100 mg
maize starch	100 mg
lactose	80 mg
aerosil	5 mg
talc	5 mg
magnesium stearate	10 mg

3. Gelatin-coated pills

A	50 mg
lactose	110 mg
maize starch	20 mg
gelatin	8 mg
calcium stearate	12 mg

4.

A	200 mg
polyvinylpyrrolidone	10 mg
maize starch	100 mg
cutina HR	10 mg

5. Injectable I.M. or I.V.

A	20 mg
sodium chloride	40 mg
sodium acetate to pH = 7	
distilled water for injection to	5 ml

6. Injectable I.M.

A	200 mg
benzyl benzoate	1 g
oil for injection to	5 ml

7. Syrup

A	5 g
tartaric acid	0.5 g
nipasept	0.1 g
saccharose	70 g
aroma	0.1 g
water to	100 ml

8. Solution

A	2 g
sorbitol	50 g
glycerine	10 g
mint essence	0.1 g
propylene glycol	10 g
demineralised water to	100 ml

9. Suppository

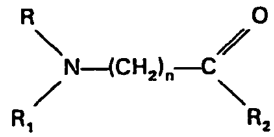
A	500 mg
butylhydroxyanisol	10 mg
semi-synthetic glycerides to	3 g

10. Rectal gel

A	100 mg
carbomer	15 mg
triethanolamine to pH 5.4	
purified water	5 g

CLAIMS

1. A derivative of an ω-amino acid which derivative is of general formula:—



I

wherein:—

R represents

a linear or branched C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11} or C_{12} alkyl radical

a linear or branched C_2, C_3, or C_4 alkyl radical substituted by a phenyl or phenoxy nucleus which may be substituted by one or two linear or branched C_1, C_2, C_3, or C_4 alkyl radicals by one or two linear or branched C_1, C_2, C_3, or C_4 alkoxy radicals or by one or two halogen atoms

a linear or branched C_2, C_3, C_4, C_5, or C_6 acyl radical substituted by a phenyl nucleus which may be substituted by one or two linear or branched C_1, C_2, C_3, or C_4 alkyl radicals by one or two linear or branched C_1, C_2, C_3, or C_4 alkoxy radicals or by one or two halogen atoms,

R_1 represents

hydrogen,

a linear or branched C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10} or C_{11} acyl radical

a linear or branched C_2, C_3, C_4, C_5 or C_6 acyl radical substituted by a phenyl nucleus which may be substituted by one or two linear or branched C_1, C_2, C_3 or C_4 alkyl radicals by one or two linear or branched C_1, C_2, C_3 or C_4 alkoxy radicals or by one or two atoms of halogen, such as fluorine, chlorine or bromine,

R_2 represents:—

a hydroxyl group

an alkoxy group R_3O— in which R_3 is a linear or branched C_1, C_2 or C_3 alkyl radical;

an amino group; and

n is 3, 4 or 5; or a pharmaceutically or veterinarily acceptable salt thereof.

2. A derivative according to Claim 1 in formula I:—

wherein

R, R_2 and n are as defined in Claim 1.

R_1 represents:—

hydrogen,

a linear or branched C_2, C_3, C_4, C_5 or C_6 acyl radical substituted by a phenyl nucleus which may be substituted by one or two linear or branched C_1, C_2, C_3 or C_4 alkyl radicals, by one or two linear or branched C_1, C_2, C_3 or C_4 alkoxy radicals, or one or two halogen atoms.

3. A derivative as claimed in Claim 1 wherein R represents:—

a linear or branched C_2—C_{10} alkyl radical;

a linear or branched C_2—C_4 alkyl radical substituted by a phenyl or phenoxy nucleus optionally substituted by a methyl or methoxy radical or by an atom of chlorine;

R_1 represents:—

hydrogen

a linear or branched C_2—C_{11} acyl radical;

a linear or branched C_2—C_6 acyl radical substituted by a phenyl nucleus which may be substituted by a methyl or methoxy radical or by an atom of chlorine;

R_2 represents:—

a hydroxyl group;

an alkoxy group R_3O in which R_3 is a linear or branched C_1—C_3 alkyl radical;

an amino group; and n 3, 4 or 5 provided that

when n has the value 4 and when R_2 represents a hydroxyl group and R_1 hydrogen, R does not represent an n-butyl or n-octyl radical

when n has the value 4 and when R_2 represents an ethoxy group and R_1 hydrogen, R does not represent an ethyl or n-butyl radical

when R represents an n-butyl radical, R_1 hydrogen and R_2 a methoxy or hydroxyl radical, n does not possess the value 3;

when R represents an i-propyl radical, R_1 hydrogen and R_2 a hydroxyl radical, n does not possess the value 5.

4. A derivative as claimed in Claim 1 wherein R represents:—

a linear or branched C_2—C_6 acyl radical substituted by a phenyl nucleus which may be substituted by a methyl or methoxy radical or an atom of chlorine;

R_1 represents hydrogen;

R_2 represents:—

a hydroxyl group;

an alkoxy group R_3O in which R_3 is a linear or branched C_1—C_3 alkyl radical;
an amino group; and
n is 3, 4 or 5.

5. A derivative as claimed in Claim 1 wherein R represents a linear or branched alkyl C_2—C_{10} group;
R_1 represents hydrogen;
R_2 represents:—
a hydroxyl group;
an alkoxy group R_3O in which R_3 is a linear or branched C_1—C_3 alkyl radical;
an amino group; and
n is 3, 4 or 5; provided that
when n has the value 4 and when R_2 represents a hydroxyl group and R_1 hydrogen, R does not represent an n-butyl or n-octyl radical;
when n has the value 4 and when R_2 represents an ethoxy group and R_1 hydrogen, R does not represent an ethyl or n.butyl radical;
when R represents an n-butyl radical, R_1 hydrogen and R_2 a methoxy or hydroxy radical, n does not possess the value and when R represents an i-propyl radical, R_1 hydrogen and R_2 a hydroxyl radical, n does not possess the value 5.

6. A derivation as claimed in Claim 1 wherein R represents:—
a linear or branched C_2—C_{10} alkyl group;
a linear or branched C_2—C_6 acyl group substituted by a phenyl nucleus;
R_1 represents hydrogen;
R_2 represents:—
a hydroxyl group;
an alkoxy group R_3O in which R_3 is a linear or branched C_1—C_3 alkyl radical and
n is 3;
provided that when R represents an n-butyl radical, R_2 does not represent a methoxy or hydroxyl radical.

7. A derivative as claimed in Claim 1 wherein
R represents:—
a linear or branched C_2—C_{10} alkyl radical;
a linear or branched C_2—C_6 acyl radical substituted by a phenyl nucleus;
R_1 represents hydrogen;
R_2 represents an amino group (—NH_2);
and n has the value 3.
provided that when R represents a dodecyl radical and R_1 hydrogen, R_2 does not represent a hydroxyl radical,
when n has the value 4 and when R_2 represents a hydroxyl group and R_1 hydrogen, R does not represent an n-butyl or n-octyl radical,
when n has the value 4 and when R_2 represents an ethoxy group and R_1 hydrogen, R does not represent an ethyl or n-butyl radical.
when R represents an n-butyl radical, R_1 hydrogen and R_2 a methoxy or hydroxyl radical, n does not possess the value 3, and when R represents an isopropyl radical, R_1 hydrogen and R_2 a hydroxyl radical, n does not possess the value 5.

8. A derivative as claimed in Claim 1 or Claim 1 wherein in formula I, R represents a C_2—C_{10} alkyl radical.

9. A derivative as claimed in Claim 1 or Claim 2 wherein, in formula I, R represents a C_2—C_5 alkyl radical.

10. A derivative as claimed in Claim 1 or Claim 2 wherein, in formula I, R represents a C_6—C_{12} alkyl radical.

11. A derivative as claimed in Claim 1 or Claim 2 wherein, in formula I, R is a C_5—C_7 radical.

12. A derivative as claimed in Claim 1 or Claim 2 wherein, in formula I, R represents a C_2—C_4 alkyl radical substituted by a phenyl or phenoxy nucleus which may themselves be substituted by a methyl or methoxy radical or by an atom of chlorine or bromine.

13. A derivative as claimed in Claim 1 or Claim 2 wherein, in formula I, R represents a C_2—C_4 acyl radical substituted by a phenyl radical itself substituted by one or two methyl or methoxy radicals or by one or two atoms of chlorine or bromine.

14. A derivative as claimed in any one of Claims 1, 2 or 8 to 13 wherein, in formula I, R_1 represents a C_2—C_5 acyl radical.

15. A derivative as claimed in any one of Claims 1, 2 or 8 to 13 wherein, in formula I, R_1 represents a C_6—C_{11} acyl radical.

16. A derivative as claimed in any one of Claims 1, 2 or 8 to 13 wherein, in formula I, R_1 represents a C_2—C_4 acyl radical substituted by a phenyl radical itself substituted by one or two methyl or methoxy radicals or by one or two atoms of chlorine or bromine.

17. A derivative as claimed in any one of Claims 1, 2 or 8 to 13 wherein, in formula I, R_1 represents hydrogen and R_2 represents an amino radical.

18. 4-n-pentylamino butanamide

19. 5-n-pentylamino pentanamide

20. 6-n-pentylamino hexanamide

21. 4-n-pentylamino butanoic acid

22. 5-(p-tolylacetylamino)pentanamide

23. 6-n-decylamino hexanamide

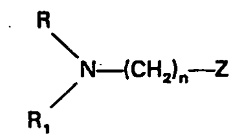
24. 6-[(2-p-chlorophenoxy ethyl)amino]hexanamide

25. 4-[(N-n-hexyl-N-4-chlorophenylacetyl)amino]butanamide.

26. A derivative as claimed in Claim 1 as hereinafter named in any one of Examples 1 to 15 or according to the formula given in any entry in Table I.

27. A derivative as claimed in Claim 1 substantially as hereinbefore described in any one of Examples 1 to 15 or any entry in Table I.

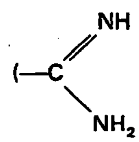
28. A process for the synthesis of a derivative as claimed in any one of Claims 1 to 27 comprising converting a derivative of formula II



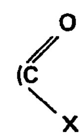
II

into a corresponding compound of formula I, R, R_1 and n having the meanings defined in Claim 1, Z representing a group which, by the action of an appropriate reactant, can be transformed into an amide function, carboxylic function or alkoxycarbonyl function (—$COOR_3$).

29. A process as claimed in Claim 28 wherein Z is an amide function, a carboxylic acid function, a nitrile function, an ester function (—COOR′, in which R′ represents either R_3, specified above, or an alkyl or phenyl radical substituted in such manner that it activates the ester in relation to the attack of a nucleophile), an amidine function

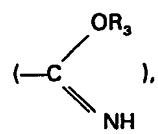


), an acid halide function

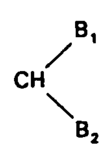


wherein

X represents a halogen), an anhydride function, an imidate function



a N-carbonylimidazol group, a trihalomethyl grouping (—CX_3, in which X represents an atom of chlorine, bromine or iodine), an oxazoline group, a hydroxymethylene group (—CH_2OH), a formyl group (—CHO) which may optionally be present in a protected form such as a cyclic or non-cyclic dithioacetal, an α, β-dihydroxyalkyl or alkenyl group (—CHOH—CHOH—R_4 or —CH=CH—R_4, in which R_4 represents a linear alkyl radical C_1—C_{20}), an acetyl group (—CO—CH_3) a 1-hydroxy ethyl group (—CHOH—CH_3), an acetonyl group (—CH—CO—CH_3) a 2-hydroxypropyl-1 group (—CH_2—CHOH—CH_3) or an atom of halogen, or wherein the grouping —CH_2—Z represents a group



in which B_1 and B_2 can be equal to or different from one another and represent nitrile, carboxylic, carbamoyl or alkoxycarbonyl (—$COOR_3$, R_3 having the values given above).

30. A process as claimed in Claim 28, wherein an amine of formula RNH—$(CH_2)_n$Z or R_1NH—$(CH_2)_n$—Z is subjected to a condensation reaction with an alkylation or acylation reactant RW, R_1W,

$\begin{matrix} R_6 \\ R_7 \end{matrix}\!\!>C{=}C{=}O$, R_8COOH, or $\begin{matrix} R_9 \\ R_{10} \end{matrix}\!\!>C{=}O$, or wherein an amine of formula $\begin{matrix} R \\ R_1 \end{matrix}\!\!>NH$

is subjected to a condensation reaction with a compound $W{-}(CH_2)_n{-}Z$ or $OHC{-}(CH_2)_{n-1}{-}Z$, as appropriate followed by a reduction of the obtained intermediate amide, imine or iminium function; R, R_1 and n in these formulae having the meanings defined in Claim 1, the groups

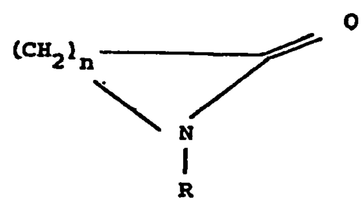
$\begin{matrix} R_6 \\ R_7 \end{matrix}\!\!>CH{-}CO$, $\begin{matrix} R_6 \\ R_7 \end{matrix}\!\!>CH{-}CH_2$, $R_8{-}CO$, $R_8{-}CH_2$ or $\begin{matrix} R_9 \\ R_{10} \end{matrix}\!\!>CH$

obtained after the condensation, followed as appropriately by a reduction, representing the group R or R_1, W representing an atom of chlorine, bromine or iodine, an O-tosyl, O-mesyl, sulphate, acyloxy or hydroxyl group, and Z being the group

$$-C{\overset{\displaystyle O}{\underset{\displaystyle R_2}{\lessgtr}}}$$

in which R_2 is as defined in Claim 1.

31. A process for the synthesis of a derivative as claimed in any one of Claims 1 to 27, wherein a lactam of formula XVIII



XVIII

in which R and n as defined in Claim 1 is converted into a derivative of formula I, under the action of a mineral acid or under the action of ammonia, an amide, an alcoholate or a hydroxide of an alkali metal.

32. A process as claimed in any one of Claims 28 to 31 substantially as hereinbefore described in any one of Examples 1 to 15.

33. A derivative as claimed in Claim 1 produced by a process as claimed in any one of Claims 28 to 32.

34. A derivative as claimed in any one of Claims 1 to 27 or Claim 33 which contains one or more assymetric carbon atoms, in the form of a racemic or non-racemic mixture of optical isomers.

35. A derivative as claimed in any one of Claims 1 to 27 or Claim 33 which contains one or more assymetric carbon atoms, in the form of an optically pure isomer.

36. A derivative as claimed in any one of Claims 1 to 27, or 33 to 35, for use in a method of treatment by therapy or surgery practised on the human or animal body.

37. A derivative as claimed in any one of Claims 1 to 27, or 33 to 35 for use in the treatment of neurological, psychic or cardiovascular deficiencies or diseases or as an anaesthetic or anthelmintic agent.

38. A pharmaceutical or veterinary formulation comprising a derivative as claimed in any one of Claims 1 to 27, or 33 to 35 formulated for pharmaceutical or veterinary use.

39. A pharmaceutical or veterinary composition comprising a derivative as claimed in any one of Claims 1 to 27, or 33 to 35 and a carrier, diluent or excipient therefor.

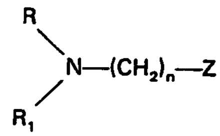
40. A composition as claimed in Claim 39 in the form of a lozenge, tablet, gelatine coated pill, pill, granule, capsule, solution, syrup, emulsion, suspension or gel.

41. A composition as claimed in Claim 39 comprising a derivative as claimed in any one of Claims 1 to 27, 33 to 35 in solution in sterile water or in an oil.

42. A composition as claimed in Claim 39 in unit dosage form wherein each unit does provide from 50 mg to 4000 mg in forms for oral administration and from 5 mg to 400 mg in forms for parenteral administration.

43. A composition substantially as hereinbefore described in any one of the Composition Examples.

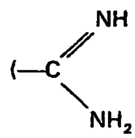
44. Amine derivative, especially for the preparation of the derivatives according to any one of the preceding Claims, characterised in that it responds to formula II:—



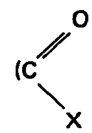
II

wherein

R, R_1 and n have the meanings given above and Z is an amide function, a carboxylic acid function, a nitrile function, an ester function (COOR', in which R' represents either R_3, specified previously, or an alkyl or phenyl radical substituted in such manner that it activates the ester in relation to the attack of a nucleophile), an amidine function

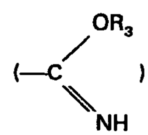


), an acid halide function

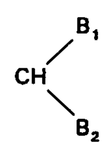


wherein

X represents a halogen such as chlorine, bromine or iodine), an anhydride function, an imidate function



or the N-carbonylimidazolyl group, it being equally possible for Z to represent a carboxylic acid precursor group like the trihalomethyl grouping (—CX_3, in which X represents an atom of chlorine, bromine or iodine), an oxazoline group, a hydroxy methylene group (—CH_2OH), a formyl group (—CHO) which can be present or not in a protected form such as a cyclic or non-cyclic dithioacetal, an α, β-dihydroxy alkyl or alkenyl group (—CHOH—CHOH—R_4 or —CH=CH—R_4, in which R_4 represents a linear alkyl radical C_1—C_{20}), an acetyl group (—CO—CH_3), an l-hydroxyethyl group (—CHOH—CH_3), an acetonyl group (—CH_2—CO—CH_3), a 2-hydroxypropyl-l group (—CH_2—CHOH—CH_3) or an atom of halogen such as chlorine, bromine or iodine, or the —CH_2—Z grouping representing the group



wherein

B_1 and B_2 can be equal or different and represent a selected function from among the following series:—

nitrile, carboxylic, carbamoyl or alkoxycarbonyl (—$COOR_3$, R_3 having the values given previously).

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